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Editorial

Benzodiazepines and Z-drugs may cause prolonged cognitive issues in young adults – are hypnotics not only a geriatric dilemma?

The risks of benzodiazepines (BZDs) in the elderly are well known. BZD use has been associated with increased risks of fallings, fractures, mobility disabilities, deteriorated activities of daily living, traffic accidents, chemical restraining and mortality [1–6]. Moreover, acute psychocognitive and motor complications related to BZDs have been shown in short-term, randomized, controlled trials [7]. In addition, the newer 'Z-drugs' such as zopiclone, zolpidem or zaleplone have not been shown to be better than conventional BZDs [8]. Even after adjusting for possible protopathic bias, long-term BZD use in the elderly has been associated with significantly higher risk of cognitive decline and dementia compared to non-users [9].

Currently, the underlying neural mechanisms linking how BZDS and Z-drugs might cause the long-term cognitive defects and dementia remain unknown. In a mice experiment [10], BZDs increased neurotoxic amyloid beta, a key protein involved in the neuropathology of Alzheimer's disease. Conversely, a human study [11] could not replicate the finding of increased neuronal protein accumulations.

Currently, geropharmacologic guidelines do not recommend the long-term BZD use in the elderly [12,13]. Moreover, practical and inexpensive interventions can be used to reduce long-term use in older adults [14–16]. Both notable and worrisome, studies have shown that in the elderly [17,18] - or in the middle-aged [19] the expected cognitive abilities are not recovered after BZD withdrawal.

But are the issues related to BZDs and Z-drugs limited only to the aged?

Authorities in many countries have accepted short-term use of short-acting BZDs in appropriate patients. Residual effects of hypnotic use on driving abilities have been reported to be conflicting or related to the half-life of drug used; while hypnotics with short-half lives have been considered safe, medium- and long-acting have not [20].

To question the idea of non-existing or low risk of cognitive residual effects in the young adults, the current issue of Sleep Medicine has published a double-blind, randomized controlled trial "Effects of zolpidem/triazolam on cognitive performance 12 h after acute administration" by Matsunaga and colleagues [21]. Their article reports the short-term follow-up results of an experimental trial being a valuable contribution to clinical BZD literature. Either a placebo or active hypnotic drug (zolpidem or triazolam) was given to healthy, young male volunteers (mean age 23.4 ± 3.2 years) in a small cohort (N = 13). The authors objectively measured the sleep parameters and the cognitive performance 12 h after administration of hypnotics in three time-points. The time-interval between individual measures was at least five days.

The results of Matsunaga and colleagues showed that sleep efficiency was increased after hypnotic drug when compared to placebo. Cognitive performance measured by a digit symbol subtraction test was deteriorated even after 12 h after hypnotic administration, while the psychomotor vigilance test remained unchanged. Therefore, the authors concluded that cognitive functions remain deteriorated 12 h after hypnotic drug administration whereas sleepiness disappears.

The experimental setting is sound, yet includes some flaws. First, the sample size is small and, thus, their study can be considered as a well-designed experimental pilot study. Second, there is a risk of bias as all participants received placebo on the first night and all three measurement points were not completely randomized and blinded followed by repetitive measuring. However, the authors had controlled these risks of biases by blinding the participants and researchers using identical tablets. Moreover, learning effects in repetitive testing was low as the tests were changed during the test protocol.

Overall, the findings by Matsunaga and colleagues are disturbing and may reveal a huge risk when employees in high risk occupations have taken hypnotics thought to be safe prior to their working shifts. According to this trial the risks of errors and accidents are increased because there is still cognitive deterioration even when not feeling tired.

To increase the external validity, trials on residual cognitive effects of BZDs and Z-drugs should be replicated in larger young and middle-aged fully randomized and controlled cohorts. Specifically, practical tests in driving, aviation and nuclear power plant simulators in addition to other high-risk occupations should be performed in order to find out the clinical meaning of the deteriorated neuropsychological tests. If the results of future trials are uniform with the results of the present study by Matsunaga and colleagues, it is time to re-write the guidelines concerning BZD use in high-risk occupations.

To understand on the biological level why cognition remains deteriorated after hypnotic exposure, the neural mechanisms and neurotoxic changes need to be explored – not only studying cerebral protein deposits – but also functionally the neuronal circuits and brain plasticity before, during and after BZD use.

Finally, benzodiazepines may be a cognitive risk factor – not only among the elderly – but in young adults as well.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2018.08.011.

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